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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

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Der Präsident des Europäischen Patentamts:
Im Auftrag

For the President of the European Patent Office

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Page 2 de l'attestation

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AGGLOMERATES BY CRYSTALLISATION

Field of the invention

The present invention describes agglomerates in crystalline form of ß-lactam compounds and a process to prepare the same.

Background of the invention

β-Lactam antibiotics constitute the most important group of antibiotic compounds, with a long history of clinical use. Among this group, the prominent ones are the penicillins and cephalosporins.

Presently, most of the β-lactam antibiotics used are prepared by semi-synthetic methods. These β-lactam antibiotics are obtained by modifying a β-lactam product obtained by fermentation by one or more reactions.

Clavulanic acid and its alkaline metal salts and esters, another type of ß-lactam compound than the penicillin and cephalosporin, act as β-lactamase inhibitors, able to enhance the effectiveness of penicillins and cephalosporins. Clavulanic acid has been applied therefore in pharmaceutical compositions to prevent inactivation of β-lactam antibiotics. For example, the antibacterial activity profile of amoxicillin is enhanced by the use of potassium clavulanate as β-lactamase inhibitor. A combination preparation of amoxicillin trihydrate with potassium clavulanate (Augmentin®) is well known.

It is generally known that antibiotic compounds in powder form are not suitable for formulation purposes, because generally these crystals perform badly as far as flowability is concerned which causes problems in the manufacturing of final dosage forms, such as tablets. Accurate dosing of the several ingredients is needed to ensure constant end product quality. In case of poor flowabilities, such accurate dosing is difficult to guarantee. Also, the needle shaped crystals, such as of potassium clavulanate, often show a low

bulk density. Thus, the contribution of such crystals to the overall volume of the final dosage form is relatively high.

To overcome these problems, often granules of compounds, for example potassium clavulanate with excipients (such as microcrystalline cellulose like Avicel® or silica like Syloid® or Aerosil®) or the granules of the compounds, for example potassium clavulanate, with active ingredients like amoxicillin trihydrate are made before producing the final formulation. Several processes are known to form such granules. For example, in case of wet granulation, potassium clavulanate can be mixed with, for instance, amoxicillin and a binding agent after which the mixture is moistened by a solvent, granulated and bounded. Before tabletting the granules with excipients, the granulates might be sieved. This wet granulation process is economically unattractive, as it uses solvents which must be recovered and/or recycled. It is labour intensive, expensive and time consuming due to the large number of processing steps such as mixing, granulating, sieving, drying etc. Moreover, in case of unstable ß-lactam compounds such as potassium clavulanate, wet granulation is problematic due to the use of a solvent and high temperature during the drying step of the process.

Another method to granulate poor flowing powders is dry granulation. As an example, the slugging process can be mentioned as described in International patent applications WO 9116893 and WO 9219227. Here, tablets of the poor flowing material with excipients are made and subsequently broken again and sieved to produce granules. Another example of dry granulation is the compaction process as described in International patent application WO 9528927. In this application, a process has been mentioned wherein compacted granules of a ß-lactam antibiotic, for example amoxicillin, and a mixture of an active ß-lactam antibiotic and a secondary pharmaceutically active agent, for example potassium clavulanate with excipients are made using roller compacting. Subsequently, the roller compacted flakes are milled, resulting in granules which can be mixed with excipients to press the final tablets. A large advantage compared to the wet

granulation is the absence of solvents. However, the dry granulation is relatively time consuming due to large number of processing steps. Also, in case of unstable products, a quality risk exists due to locally high temperatures in the process, e.g. due to abrasion. In case the material is hygroscopic, such as potassium clavulanate, another disadvantage is the handling of the dried crystals before and during the granulation process. During this handling, the product might attract water leading to unwanted degradation reactions. Also a major disadvantage of roller compacted products is the relatively large amount of fines which should be removed using sieving techniques to improve the flowability of such products.

Furthermore, difficulties one may encounter by using dry granulation are:

- a lot of dust is produced during the slugging or roller compaction process and in some cases, for example such as amoxicillin, this dust sticks to the coarser particles and can not be separated by currently applied vibrating sieves,
- dust may deteriorate the flow properties of agglomerates,
- dust is also responsible for air born ß-lactam antibiotics particles which can cause allergic reaction.

Granules of the active ingredient in the presence of excipients are produced by the process mentioned above. It would be advantageous to have the possibility to produce granules of the pure active ingredient. In that case, the production process can be more flexible and possibly overall less excipients are necessary. Also the production of final dosage forms will be more flexible. In case of hygroscopic substances such as potassium clavulanate, however, it will be difficult to granulate using one of the above processes without the presence of excipients like microcrystalline cellulose or silica, as the latter are known to protect the hygroscopic potassium clavulanate by removing the free water from it and, thus, keeping the water activity of such compositions low. However, in the International patent application WO 9733564 a method has been mentioned in which granules of a pure active ingredient, without the presence of excipients, are made by

extrusion. Here, a paste is made of the crystalline powder by adding a liquid wherein the powder is insoluble or slightly soluble. The paste is needed then and extruded in a double screwed extruder, after which the granules are dried. The process again is not suitable for unstable products, as locally the temperature in the extruder is high (up to 80°C). Also, this wet material should be dried at elevated temperatures.

Another method to improve the flowability of needle shaped crystals, especially in the case of potassium clavulanate, is to agglomerate them during crystallisation to the so-called rosette form as described in European patent EP 277008 B1. In this case, a plurality of needle crystals radiate out from a common nucleation point. The rosettes show an increased flowability compared to the needles. However, a large disadvantage of these types of granules is the inclusion of impurities, leading to a decreased chemical quality of the product. Also, the included impurities probably increase the degradation rate of the ß-lactam compound, thus resulting in an even worse chemical quality during storage. The term agglomerate as used in the present application, refers to clustering of the crystals of a compound.

The object of the invention is to provide a valuable form of ß-lactam antibiotic compound and a process which overcomes most of the above mentioned disadvantages.

Surprisingly, it has been found that novel agglomerates in crystalline form of ß-lactam antibiotics in a liquid phase are produced through a crystallisation process when a solution of at least one ß-lactam compound in a solvent or in a mixture of solvents under stirring is mixed together with one or more non-solvents, optionally containing water.

Summary of the invention

The present invention provides agglomerates in crystalline form comprising one or more ß-lactam compounds having at least one ß-lactam compound of a high water affinity, and optionally contain one or more excipients. Preferably, said agglomerates comprise clavulanic acid or a pharmaceutically acceptable salt thereof like potassium clavulanate. Further, the agglomerates comprising potassium clavulanate may contain amoxicillin as the active ß-lactam antibiotic compound.

The excipients are microcrystalline cellulose, preferably Avicel®, or silica, preferably Syloid® or Aerosil®.

The said agglomerates can also be of sterile form.

The new agglomerates are of an average particle size between about 1 µm and 1500 µm, preferably between about 500 µm and 1500 µm, more preferably between 800 µm and 1200 µm or between 1 µm and 200 µm.

Furthermore, a process to prepare said agglomerates has been provided for. The agglomerates are produced in a liquid phase medium, which process involves mixing together a solution or suspension of at least one ß-lactam compound in a solvent or in a mixture of solvents under stirring with one or more non-solvents, optionally containing water. The volume ratio of the solvent to the non-solvent is about 0.05 to 10 wt%. Preferably, the solvent is water and the non-solvent is a ketone, like acetone, methylethylketone, methylisobutylketone or an ester, like methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate or an alcohol, like 1-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol or a mixture of these solvents. Specifically, the solvent is water or ethanol and the non-solvent is acetone or ethyl acetate. It is possible also to add other ingredients in one of the streams (solvent, non-solvent or mixture thereof), either suspended or dissolved.

During the preparation of the agglomerates, one or more stirring devices are used to crystallise, agglomerate and deagglomerate, or to crystallise and

agglomerate, or to crystallise and deagglomerate the ß-lactam compound and optionally classification and blending with excipients and/or another ß-lactam compound in a batch or continuous operation in one or more reaction vessels or in one integrated step. Furthermore, the operation is performed by applying stirring devices in one or more vessels, an in-line mixer or a combination thereof. Furthermore, it is possible to use a high shear mixer during the preparation of these agglomerates.

The agglomerates of various particle sizes are regulated by further using a combination and permutation of different stirring devices and their speed, the type and amount of the solvents used and the way of mixing of the solvents.

Agglomerates of potassium clavulanate of the present invention show a high stability and a low level of hygroscopicity.

The agglomerates, prepared according to the present invention, with one or more pharmaceutical acceptable excipients can be used for pharmaceutical formulations.

A pharmaceutical formulation comprising amoxicillin, preferably amoxicillin trihydrate and the crystalline agglomerates of potassium clavulanate of the said invention and optionally one or more pharmaceutically acceptable inert excipients can be prepared.

Also, a pharmaceutical formulation, comprising crystalline agglomerates of amoxicillin trihydrate and potassium clavulanate and one or more pharmaceutically acceptable inert excipients can be made.

The agglomerates, prepared according to the present invention, are suitable to prepare oral dosage forms such as tablets, capsules, syrups, sachets, dry instant or ready to use and multiple or single dose. According to another embodiment of the invention, the oral dosage form, comprising agglomerates or granules of amoxicillin with or without one or more excipients can also contain a β-lactamase inhibitor such as potassium clavulanate, preferably in the agglomerated form. Said agglomerates can also be used in Dose Sipping devices.

Detailed description of the invention

The present invention provides economically interesting agglomerates in crystalline form of a ß-lactam compound. The ß-lactam compounds are for instance clavulanic acid but one can also think of amoxicillin or ampicillin. The compound can be in the salt form, such as amine or alkaline metal salt. Preferably, agglomerates of potassium clavulanate are produced.

The agglomerates of said invention have an average particle size between about 1 μm and 1500 μm, preferably between about 500 μm and 1500 μm, or between 1 μm and 200 μm.

A process for the preparation of the agglomerates, wherein one or more ß-lactam compounds with or without excipients are used, consists of a crystallisation procedure to build up agglomerates. The process comprises mixing together a solution or suspension of one or more ß-lactam compounds in a solvent or in a mixture of solvents with one or more non-solvents under stirring. The combination of solvent and non-solvent can result in an emulsion.. The non-solvent can optionally contain water or ethanol. Thereafter, the agglomerates are filtered off, washed and dried. The agglomerates, thus produced in high yield, maintain the quality criteria set and are highly suitable for further processing. For the present application, a non-solvent is defined as a liquid in which the ß-lactam compound does not dissolve or dissolves only poorly

More in detail, the ß-lactam compound, for instance potassium clavulanate, is dissolved in an appropriate solvent or a mixture of (partly) miscible solvents, such as water, alcohols, like ethanol, methanol, 1-propanol, 2-butanol, 2-methyl-propanol, ketones, like acetone, methylethylketone, methylisobutylketone, or an ester, like methyl acetate, ethyl acetate, butyl acetate. Sometimes an emulsion is formed during the agglomeration process. The way of dissolution will be known to those skilled in the art and will depend on the stability of the ß-lactam compound in the solvent or in a

mixture of solvents. In case water is used as the only solvent for the dissolution of potassium clavulanate, residence time and temperature should be as low as possible and a technique such as in-line mixing, for example a static mixer, can be attractive. If for example acetone is present, a residence time of several hours might be acceptable.

The ß-lactam compound, for example potassium clavulanate, present in the solvent dissolved or in suspension or in both forms, is contacted with a non-solvent such as ketone, like acetone, methylethylketone, methylisobutylketone, or an ester, such as methyl acetate, ethyl acetate, butyl acetate or a mixture thereof, or an alcohol such as 1-propanol, 2-butanol, 2-methyl-propanol optionally containing a solvent for the ß-lactam compound, such as for potassium clavulanate, like water or an alcohol, such as methanol or ethanol. The overall volume of solvent to non-solvent depends on the combination of solvents and on the desired agglomerate diameter, but generally lies within 0.05-10%. Also, it is possible to adjust this ratio by adding some solvent to the crystalliser before or during the process. This ratio will influence the average diameter of the agglomerates: the higher the relative volume of the solvent, the larger the agglomerates will be.

Several methods of mixing can be applied and will be known to those skilled in the art. For example, the solution of the ß-lactam compound, for instance a potassium clavulanate solution and the non-solvent can be added simultaneously to the crystalliser or the solution of the ß-lactam compound, for instance a potassium clavulanate solution can be added to the non-solvent or the non-solvent can be added to the solution of the ß-lactam compound, for instance a potassium clavulanate solution. The temperature should be kept below 50°C. The use of seeding material can also be advantageous to enhance the agglomeration process.

The method of agitation is determined by the desired agglomeration size of the ß-lactam compound. In case of relatively large agglomerates (order of magnitude of 1000 μm), the agitation should be moderate. For example a common turbine agitator or pitched blade agitator can be used. Here, the

general scales up parameters for agitation applies: the diameter of the blades versus the diameter of the vessel should be between 0.2-0.9, preferably between 0.2 -0.5, depending on the type of agitator used. The rotational speed (and thus shear), tip velocity and power input determine the agglomerate size and can be used as control parameters. In case the desired agglomerate diameter is small, for example 50-100 μm, high speed agitators, such as toothed disks or rotor-stator mixers with multiple stage mixing/shearing action could be used. Also, it is possible to use in-line high shear mixers, with the advantage of short residence times. If needed, a recycle loop can be applied over such an in-line system. Another possibility is to combine a moderate shear mixer with a high shear mixer or a mill. For example, the agglomerates with a diameter of the order of magnitude of 1000 μm can be deagglomerated during the crystallisation using a high shear mixer, which is situated in the same crystalliser (such as mounted in the bottom) or as a separate unit after the crystalliser. Also, for example a colloid mill can be placed after the crystalliser for the same purpose. Moreover, the simultaneous crystallisation/agglomeration technique can be combined using ultrasonic crystallisation. This technique has been described for instance in *Pharmaceutical Technology Europe*, 9(9), 78 (1997).

Generally, the residence time in the crystalliser and/or deagglomerator is determined by the desired average diameter of the agglomerates. For purposes of precipitation/crystallisation, long ageing times are not needed, as the crystals are formed immediately after contact with the non-solvent. For agglomeration and deagglomeration, however, probably a certain minimum residence time will be needed, depending on parameters such as mixing time and volume of the vessel.

One of the embodiments of the invention is to have the excipients included in the agglomerates by addition of the same before, after or during the precipitation and/or agglomeration, such as cellulose, preferably microcrystalline cellulose, more preferably with a water activity < 0.2 at 25°C, most preferably PH112. Also, amorphous silica (Syloid®) or colloidal

silicon dioxide (Aerosil®) is used as excipient. All methods of mixing are possible: for example the excipient can be added before, simultaneously or after the addition of the ß-lactam compound solution or (partly) suspension to the crystalliser. The excipients can be added as dry matter, suspended or dissolved in a solvent, preferably one of the solvents (or a mixture thereof) which is already used in the agglomeration process. An extra advantage of the addition of such excipients is the positive influence on the agglomeration formation, as they can act as some kind of seeding material.

Another embodiment of the present invention is that the crystallisation and agglomeration can occur in the presence of another active ß-lactam ingredient, for example amoxicillin trihydrate besides potassium clavulanate. The amoxicillin can either be added as a solution or suspension leading to co-crystallisation, similar to the agglomeration in presence of excipients.

The agglomerates of the present invention are not of the rosette type: they consist of small crystals clustered together in a random spherical order. Depending on the method of agitation, the agglomerate size can easily be adjusted between about 1 and 1500 μm and also related small particles as with average size of 1-200 μm or related large particles with an average size of 1000 μm may be prepared. Compared to, for example, dry compaction, the amount of fines that either must be discharged of or that must be recycled, is small. The agglomerates can easily be separated by for example, filtration and subsequently dried using conventional methods such as tumbling drying. It is also possible to include a classification process. For example, agglomerates of the desired size can be selectively removed from the crystalliser using gravity and/or a sieve. Fines which can be removed by sieving as well, can be recycled, either by addition in suspension or solution to the next batch.

If necessary, pH-adjustment in order to increase the stability of the end product can be achieved by adding an acid or base to the solution or the non-solvent before contacting the streams of solvents containing the ß–lactam compound and the non-solvent. Also, acid or base can be added during the precipitation/crystallisation/ agglomeration process or even after the process.

Surprisingly, the process of the present invention produces agglomerates with a high bulk density, an improved flowability and less compressibility. For example, potassium clavulanate agglomerates produced have a loose bulk density between about 0.30 and 0.60 with an average of about 0.50 g/ml, and a tapped bulk density between about 0.50 and 0.90 g/ml with an average of 0.70 g/ml and a compressibility between 15 and 40% with an average of 25%.

Due to the excellent flowability of the agglomerates prepared using the above method, they can be used for, for example, direct compression of tablets without the need for further pre-granulation. Moreover, due to the decreased surface area of the agglomerates, the degradation caused by chemical reactions on the surface (e.g. with water) is significantly reduced. The hygroscopicity of clavulanate, a well-known property which causes difficulties with the handling of potassium clavulanate needle shaped crystals, is also reduced. The level of impurities in the agglomerates is also equal to or even lower than in case of conventional needles. As the bulk density increases significantly, large advantages can be achieved in the transportation as well as in the tabletting process: the final tablet volume can decrease significantly when using agglomerates compared to using needles.

The energy consumption of the present process is low, as the crystallisation process which is commonly present in the down stream process of pharmaceuticals can be combined with the agglomeration process. Moreover, it is possible to combine the usual operations comprising purification and separation by precipitation or crystallisation, agglomeration and deagglomeration, classification and blending with e.g. excipients in one unit. The temperatures can be kept below 50°C during the complete agglomeration process, excipients-free agglomerates can be produced and handling of dry solids before the granulation does not occur, which is an important advantage in case of hygroscopic materials. The solvents needed for the agglomeration can easily be recycled, possibly without the need for purification. Moreover, the possibility to make pure agglomerates of an

unstable and hygroscopic product such as potassium clavulanate is highly attractive.

The agglomerates of the present invention can be used for all formulations to produce chew, swallow, disperse, effervescent or normal tablets of all sizes, forms and weights, also to fill hard gelatine capsules and to formulate dry syrups and for administering drugs with the help of a dose sipping device. These agglomerates can also be used, for instance, in a pharmaceutical composition as a tablet of amoxicillin trihydrate produced from agglomerates of amoxicillin trihydrate and potassium clavulanate. For the preparation of sterile agglomerates, the solution of the ß-lactam compounds, solvent and non-solvens are sterilely filtered prior to crystallisation/agglomeration. Further, the sterile agglomerates are another aspect of the present invention

The invention will now be described with reference to the following Examples, which are not to be constructed as being limiting on the invention, and are provided purely for illustrative purposes.

Example 1

Preparation of agglomerates of potassium clavulanate (batch process)

In a 5-litre flask equipped with a mechanical stirrer, a thermometer and inlet for nitrogen, 4 litres of acetone were placed. A solution of potassium clavulanate (60 g.) in a mixture of water/acetone (120 g, 1:1 w/w) was added in 30 min at 20°C under stirring.

The solid material was filtered off and dried in vacuum at 30°C during 2-3 hours to give agglomerates of potassium clavulanate with an average diameter in the range of 100-1000 μm and a yield of 98% .

Example 2

Preparation of agglomerates of potassium clavulanate (semi-continuous process)

In a 2-litre flask equipped with a mechanical stirrer, a thermometer and inlet for nitrogen, acetone (1000 ml) and water (10 ml) were placed. Simultaneously a solution of potassium clavulanate (60 g) in a mixture of water/acetone (120 g, 1:1 w/w) and acetone (4000 ml) was added in about one hour, while agitating.

During the addition the content of the vessel was kept at about 1800 ml by periodically removing suspension through an outlet.Thereafter, the solid material was filtered off, washed with dry acetone and dried in vacuum at 30°C during 2-3 hours to yield potassium clavulanate agglomerates with an average diameter in the range of 500-1500 μm.

Example 3

Preparation of agglomerates of potassium clavulanate by using a turbine stirrer without baffles in the reaction vessel

Acetone (300 ml) and water (3 ml) were placed in a glass cylinder (100 mm in diameter, 150 mm height) equipped with a turbine stirrer (40 mm diameter), a two dropping funnels and a nitrogen inlet tube. Under stirring (900 rpm) simultaneously a solution of potassium clavulanate (30 g) in a water/acetone mixture (60 g, 1:1 w/w) and acetone (2000 ml) were added.

During the addition, the contents of the vessel were kept on about 900 ml by removing a part of the contents with the help of an outlet. After the completion of the additions, the solid material was filtered off, washed with dry acetone and dried in vacuum at 30°C. Agglomerates of potassium clavulanate with an average particle diameter of 1000 μm were obtained in 98 % yield.

Example 4

Preparation of agglomerates of potassium clavulanate by using turbine stirrer with baffles in the reaction vessel.

The experiment was repeated as described in Example 3, but using a vessel with four baffles with a width of 10 mm. Potassium clavulanate agglomerates with an average diameter in the range of 500-1000 μm were obtained.

Example 5

Preparation of agglomerates of potassium clavulanate by using a Ultra-Turrax mixer.

Acetone (500 ml) and water (5 ml) were placed in an one litre 4-necked round-bottom flask equipped with a thermometer, Ultra-Turrax mixer (type T25 and shaft S25N-18G), two dropping funnels an a nitrogen inlet tube.

Under mixing (8000 rev/min) simultaneously a solution of potassium clavulanate (30 g.) in a water/acetone mixture (60 g. 1:1 w/w) and acetone (2000 ml) was added in one hour at 15-20°C. During the addition, the contents of the vessel were kept between 700 and 800 ml by removing a part of the content with the help of an outlet.

After the completion of the additions, the solid material was filtered off, washed with acetone and dried in vacuum at 30°C. Agglomerates of potassium clavulanate with an average diameter in range of 50-250 μm were obtained.

Example 6

Preparation of agglomerates of potassium clavulanate by using Silverson L4RT mixer.

The experiment was repeated as described in Example 5, but using a rotor-stator type high shear mixer (Silverson mixer with emulsion screen, i.e. a screen with spherical pores of about 1.5 mm) at 3000 rev/min.

Agglomerates of potassium clavulanate with an average diameter in the range of 10-200 μm were obtained.

Example 7

Preparation of agglomerates of potassium clavulanate in ethyl acetate

Ethylacetate (400 ml) and water (1 ml) were placed in a glass cylinder (100 mm in diameter, 150 mm height) equipped with a turbine stirrer (40 mm diameter), a two dropping funnels and a nitrogen inlet tube. Under stirring (900 rpm) at the same time a solution of potassium clavulanate (10 g) in water (10 ml) and ethyl acetate (600 ml) were added.

After the completion of the additions the solid was filtered off, washed with dry ethyl acetate and dried in vacuum at 30°C to give agglomerates with an average diameter in the range of 500-1500 μm.

Example 8

Comparison of agglomerates and needles of potassium clavulanate, optionally mixed with Avicel PH112.

The agglomerates of potassium clavulanate were prepared as described in Example 6, but using a Silverson mixer with general purpose disintegrating screen, i.e. a screen with square holes with a diameter of about 2.5 mm. In a 2- litre flask equipped with the Silverson mixer, a thermometer and inlet for nitrogen acetone (1000 ml) and water (10 ml) were placed. Under mixing

(3400 rev/min) simultaneously a solution of potassium clavulante (120 g) in a mixture of water/acetone (240 g, 1:1 w/w) and acetone (8000 ml) were added at 15-20°C. During the addition the contents of the vessel was kept at about 1800 ml with an outlet. After completion of the additions the solid was filtered off, washed with acetone and dried in vacuum at 30°C during 2-3 hours to give agglomerates with an average diameter in the range of 40-200 μm.

Needles of potassium clavulanate were prepared by suspending diclavulanate salt of bis(2-dimethylaminoethyl) ether (100 g) in acetone (3350 ml) and water (50 ml). Under stirring a solution of potassium 2-ethylhexanoate (1450 ml, 0.34 M) in acetone at 5-10°C was added. After 1 hour stirring the mixture was filtered off, washed with dry acetone and dried in vacuum during 18 hours at room temperature to give 81.2 g of potassium clavulanate needles.

A comparison of physical properties of potassium clavulanate in agglomerated and needle form, optionally mixed with Avicel PH112 in a ratio of 70 : 30 w/w% have been described in Table 1.

Material	Loose bulk density	Tapped bulk density	Compressibility	Particle size distribution
Agglomerates of potassium clavulanate	0.49g/ml	0.68g/ml	28%	between 1 and 200μm
Needles of potassium clavulanate	0.18g/ml	0.36g/ml	50%	between 5 and 75μm
Agglomerates of potassium clavulanate mixed with Avicel PH112	0.43g/ml	0.61g/ml	29%	Not determined
Needles of potassium clavulanate mixed with Avicel PH112	0.20g/ml	0.40g/ml	50%	Not determined

Table 1

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CLAIMS

1. Agglomerates in crystalline form comprising one or more ß-lactam compounds, wherein at least one ß-lactam compound has a high water affinity, and optionally containing one or more excipients, with the proviso that the rosette-like crystalline form of potassium clavulanate is excluded.

2. Agglomerates according to claim 1, wherein at least one ß-lactam compound is clavulanic acid.

3. Agglomerates according to claim 2, wherein the ß-lactam compound is potassium clavulanate.

4. Agglomerates according to claim 3, consisting of only potassium clavulanate.

5. Agglomerates according to claim 3 further comprising amoxicillin.

6. Agglomerates according to anyone of the claims 1-3 or 5, wherein the excipients are microcrystalline cellulose, preferably Avicel®, or silica, preferably Syloid® or Aerosil®.

7. Agglomerates according to anyone of the claims 1-6, wherein the agglomerates have an average particle size between about 1 μm and 1500 μm, preferably between about 500 μm and 1500 μm, or between 1 μm and 200 μm.

8. Agglomerates according to anyone of the claims 1-7 in sterile form.

9. A process for the preparation of crystallised agglomerates as defined in anyone of the claims 1-8, wherein the agglomerates are produced in a liquid phase by applying stirring devices.

10. A process according to claim 9, wherein the liquid phase comprises a solution or suspension of at least one ß-lactam compound in a solvent or in a mixture of solvents together with one or more non-solvents, optionally containing water.

11. A process according to claim 10, wherein the ratio of the solvent to non-solvent is about 0.05 to 10 wt%.

12. A process according to claim 10 or 11, wherein the non-solvent is a ketone, like acetone, methylethylketone, methylisobutylketone or an ester, like methyl acetate, ethyl acetate, isopropyl acetate, butyl acetate or an alcohol, like 1-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol or a mixture of these solvents.

13. A process according to anyone of the claims 10-12, wherein one or more stirring devices are used to crystallise, agglomerate and/or deagglomerate the ß-lactam compound and optionally classification and blending with excipients and/or another ß-lactam compound in a batch or continuous operation, in one or more units.

14. A process according to anyone of the claims 10-13, wherein the process is performed by applying stirring devices in one or more vessels, an in-line mixer or a combination thereof.

15. A process according to anyone of the claims 10-14, wherein a high shear mixer is used.

16. A process according to anyone of the claims 10-15, characterised by the preparation of agglomerates with various particle sizes, by further using a combination and permutation of different stirring devices and their speed, the type and amount of the solvents used and the way of mixing of one or more solvents and non-solvents.

17. A process according to anyone of the claims 10-16, wherein the solvent is water or ethanol and the non-solvent is acetone or ethyl acetate.

18. A pharmaceutical formulation comprising the agglomerates of anyone of the claims 1-8 and one or more pharmaceutical acceptable excipients.

19. A pharmaceutical formulation comprising amoxicillin, preferably amoxicillin trihydrate and the crystalline agglomerates of potassium clavulanate of claim 4, and optionally one or more pharmaceutically acceptable inert excipients.

20. A pharmaceutical formulation, comprising a mixture of amoxicillin trihydrate and crystalline agglomerates of potassium clavulanate and one or more pharmaceutically acceptable inert excipients of claim 3.

21. Pharmaceutical dosage forms comprising a pharmaceutical formulation of anyone of the claims 18-20.

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AGGLOMERATES BY CRYSTALLISATION

ABSTRACT

The present invention describes novel agglomerates in crystalline form of ß-lactam compounds. Furthermore, a process for the preparation of said agglomerates, wherein a solution or suspension of at least one ß-lactam compound in a solvent or in a mixture of solvents under stirring is mixed together with one or more non-solvents, optionally containing water, has been described.